REMARKS

Status of the Claims

Claims 1-2 and 5-34 were rejected in the Office Action of December 15, 2004. Claims 5, 6-8, 17, and 33 have been amended. Claim 12 has been canceled without prejudice as being identical in scope to the claim that it depends from (Claim 9). Upon entry of this response claims 1-2, 5-11, and 13-34 will be pending.

No new matter has been added.

Summary of the Invention

Direct DNA administration of DNA constructs that include regulatory elements that function in macrophages and cells of macrophage derived lineage can be used to deliver proteins to macrophage cells, cells of macrophage derived lineage and lymphnodes. Through the use of regulatory elements (*e.g.* promoters and/or macrophage specific promoters), the present invention can be used to deliver proteins to the specific cells and cell types described above. This discovery allows the user of the present invention to target lymphnodes.

Some embodiments of the present invention provide methods of delivering a protein to a macrophage cell or a cell of macrophage derived lineage of an individual comprising the steps of: administering to the individual at a site on the individual's body, a DNA molecule, wherein the DNA molecule is a plasmid comprising a nucleotide sequence that encodes the protein, wherein the DNA molecule is operably linked to a macrophage specific promoter (*e.g.* a catalase promoter, a CD156 promoter, a M-CSFR promoter, a p73 promoter, an FcγRI promoter, or other macrophage specific promoter) and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage. The DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where the nucleotide sequence is expressed to produce the protein in the macrophage cell and/or the cell of macrophage derived lineage. (Claims 1 and 5).

The targeting that has been problematic for other types of gene delivery do not plague this aspect of the present invention because when DNA is administered (*e.g.*

intramuscular administration) to the individual, the DNA is taken up by the macrophage cells or cells derived from a macrophage.

Macrophage cells take up the DNA molecule with a macrophage specific promoter the protein that is expressed by the DNA molecule is delivered to a lymphnode (Claim 11). Since the macrophage cells are taken up by the lymphnode, a lymphnode can easily be eliminated by administering a DNA molecule that encodes a protein that would eliminate the lymphnode.

Some embodiments of the present invention relate to methods for modulating and/or inducing an individual's immune response. Macrophage cells are important contributors to an individual's immune system. Because macrophage cells take up the DNA that is being administered some aspects of the invention provide for modulating or inducing the individual's immune system.

Rejections under 35 U.S.C. § 112

Claims 1-2, 6-8, 18-24, 29 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, at the time the application was filed, had possession of the claimed invention. The Office alleges

> The specification as filed does not provide sufficient description of the structure and identifying characteristics of a sufficient number of species of the genus claimed...It is emphasized that the claimed invention encompasses promoter sequence of any gene that is specifically expressed in a macrophage cell which as has specialized function and the genes that will be specifically expressed in this cell will be very different from each other and therefore, the genus of macrophage specific promoter will represent multiple subgenera that will have unrelated structure and function...Such functional characteristics do not and cannot differentiate one species from the other

> species or from other subgenera or subspecies because all of them will have this functional characteristics.

(Office Action, pages 2-3). Applicants respectfully disagree.

Applicants clearly had possession of the invention at the time the Application was filed because Applicants disclosed numerous examples of macrophage specific promoters and one of skill in the art would understand that the present invention includes those promoters as well as any other promoter that is macrophage specific. The Office has failed to give provide adequate evidence to demonstrate that the claims fail to satisfy the written description requirement. On the contrary, the Office's argument that Applicants have failed to satisfy the written description requirement actually support the fact that the specification does in fact comply with the written description requirement. There is no question that a promoter is a nucleotide sequence of a nucleic acid molecule. As discussed above, the Office admits that the all the macrophage specific promoters will have the same function. This function is what defines whether or not a promoter from a gene is covered by the claim. For the Office to say that "functional characteristics do not and cannot differentiate one species from other species" would render the guidelines for written description meaningless. The MPEP states:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

(MPEP § 2163). Applicants have shown that the invention is complete by disclosing the function of the promoter and then also providing five examples of promoters that are macrophage specific. Applicants ***are not*** required to supply every macrophage specific promoter that is either known or available in the art, rather Applicant is only required to disclose a representative number of species. The MPEP states

> "representative number of species" means that the species which are adequately described are representative of the entire genus.

(MPEP § 2163). The species described in the present application are adequate to describe the genus. One of ordinary skill in the art would know and understand that Applicants had possession of the entire genus of macrophage specific promoters for the methods described in the pending claims. One of skill in the art would understand that the promoter would comprise a nucleotide sequence and be macrophage specific. As discussed in previous responses and declarations one of ordinary skill in the art would be able to determine if a promoter is macrophage specific without undue experimentation. The Office dismisses the relevance of the declaration submitted by Dr. Weiner, which states:

> One of ordinary skill in the art would be able to determine whether a promoter is macrophage specific without undue experimentation by using routine, well known techniques.

The Office dismisses this declaration as stating that it does not "provide any evidence except for making a conclusory remark." Applicants respectfully disagree. It is well settled that the question of whether a specification provides an adequate written description of the subject matter of the claims is an issue of fact. The Office was in error when he stated that the Weiner declaration, which attempted to shed light on whether the specification adequately described the claimed subject matter, provided evidence. The Office has not accepted the Weiner declaration as offering factual evidence on the adequate written description issue. In fact, the Weiner declaration provides a clear factual statement. The declaration must be read as offering factual evidence in an attempt to explain whether one of ordinary skill in the art would have understood that applicants were in possession of the claimed invention at the time the application was filed. The declaration demonstrates that one of ordinary skill in the art would be able to determine if a promoter is macrophage specific, which must be accepted as fact by the Office, unless the Office has evidence to rebut the statement in the declaration. Accordingly, one of skill in the art would know that a macrophage promoter would have a nucleotide sequence (structure) and be macrophage specific (function). These two elements can be used to satisfy the written description requirement. Applicants are not required to provide a core structure beyond a nucleotide sequence nor are Applicants required to

provide a consensus sequence of what makes a promoter macrophage specific as the Office alleges. Rather, Applicants are only required to convey possession of the invention to one of ordinary skill in the art by showing that one of skill in the art would understand that the Applicants had possession at the time the application was filed. Clearly, Applicants had possession because a representative number of species are described and one of skill in the art would be able to determine what species of promoters are included in the genus and which are not without an undue burden. Applicants' disclosure demonstrates possession of the claimed invention.

Furthermore, one of skill in the art would ***recognize*** that Applicants were in possession of the necessary "common attributes or features" of the genus. The "common attributes or features" of members of the genus are that the promoters are macrophage specific and they come from a human gene. These features are unambiguous and is discussed in the specification (see, for example, p. 11, lines 16-18).

The Office is respectfully reminded that, "[d]escription of a representative number of species ***does not require*** the description to be of such specificity that it would provide individual support for each species that the genus embraces." (M.P.E.P. § 2163, emphasis added). Therefore, in addition to the species described in the present Application, Applicants were in possession of the genus that includes promoters that are macrophage specific in a human.

The courts have stated, for example,

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention. (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement…by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention."

(*University of California v. Eli Lilly and Co* (CA FC) 43 USPQ2d 1398, @1404, citations omitted). The specification describes the invention specifically and with "sufficient

detail" that one skilled in the art would conclude that Applicants were in possession of the invention. Accordingly, Applicants have demonstrated possession of the invention and satisfied the requirements for Written Description. Applicants have described what is meant by a macrophage specific promoter (regardless of its origin) and one of skill in the art would, therefore, know that Applicants were in possession of the claimed invention when the application was filed.

Furthermore, as discussed previously, the present invention is not claiming "macrophage specific promoters," *per se*. Rather the pending claims that include the term "macrophage specific promoter" only refer to one element of the nucleotide sequence that is being ***used*** in the claimed method.

In view of the foregoing, Applicants respectfully request that the rejection alleging that the claims fail to satisfy the Written Description requirement be withdrawn.

Claims 1-2 and 5-8 stand rejected under 35 U.S.C. § 112, first paragraph because allegedly the specification, while being enabling for a method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage *in vitro* or *in vivo*,

> comprising intramuscular administration of a plasmid DNA molecule wherein a nucleotide sequence encoding the protein is operably linked to a macrophage specific promoter and a polyA signal that is functional in macrophage cell or a cell of macrophage derived lineages, wherein said macrophage specific promoter is selected from the list a catalase promoter, a CD156 promoter, a M-CSFR promoter, a p73 promoter and an FcγRI promoter, wherein said plasmid molecule is taken up by a macrophage cell or a cell of macrophage derived lineage and wherein said nucleotide sequence is expressed to produce said protein in said macrophage cell or said cell of macrophage derived lineage does not reasonably provide enablement for other embodiments.

(Office Action, page 3-4). Applicants respectfully disagree.

Claims 9-31 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Claims 1-2 and 5-8, 9-34 and new claims 32-35, which depend on claims 1, 5, and 9 respectively are enabled. The present Application supplies working examples and sufficient guidance that one of skill in the art would ***not*** have to perform undue experimentation to practice the claimed invention.

The Office alleges in support of its enablement rejection is based upon the unpredictability of targeted gene delivery and gene therapy as discussed in the Crystal and Anderson references (Office Action, pages 4-5).

As an initial matter, Applicants have amended claim 5 and it corresponds to the subject matter indicated to be in the present office action. Accordingly the claims that depend from claim 5 (Claims 6-8, 17, and 33) are also enabled. Applicants respectfully assert that the remaining claims are also enabled for the reasons set forth below.

Applicants respectfully assert that the Office is not following the well established standards for determining whether or not an invention is enabled.

> A specification disclosure...***must be taken*** as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support ... As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with ***acceptable evidence or reasoning*** which is inconsistent with the contested statement."

(M.P.E.P. § 2164.04, citations omitted, emphasis added). Throughout prosecution of the present application, the Office has failed to provide "acceptable evidence or reasoning" that demonstrates doubt to the objective truth of the statements contained in the specification and claims. The Office has failed to explain, in view of the differences between the cited references and the present invention, why the cited references demonstrate that the present invention is not enabled.

In the present rejection, the Office refers back to two previous office action (mailed March 27, 2003 and August 8, 2003) in support of the current rejection. In those rejections the Office cites three references (Crystal R.D., *Science* 270:404-410; Anderson WF. *Nature* 392 (Supp):25-30; and Clay TM *et al. Pathology Oncology Research* 5:3-15) to demonstrate the unpredictability of the prior art and that the present invention is not enabled. However, as Applicants have stated previously (See Responses filed June 25, 2003 and October 8, 2003) the references do not discuss unpredictable features that are relevant to the present invention. Even in the present Office Action, the Office has still failed to explain how the references apply to the pending method claims, which are not analogous to what is described in the cited references. The three references discuss gene therapy, viral vectors and the ability of the vectors to sustain long-term expression of the protein in question. ***None of these factors are relevant to the pending claims.*** As discussed above, the pending claims are related to methods of delivering a protein to a macrophage cell or a cell of macrophage derived lineage, methods of delivering a protein to a lymphnode, methods of inducing an immune response, methods of modulating an individual's immune response, and methods of delivering a desired protein to an individual. The methods use the overall same technique whereby a DNA molecule that is linked to a promoter, in some embodiments a macrophage specific promoter, is administered and will be taken up by macrophage cells, cells of macrophage derived lineage, and lymphnodes, or modulate/induce an immune response where the coding sequence linked to the promoter will be expressed. None of the references cited by the Office discuss any challenges relating to these processes. Applicants respectfully request that if the rejection is maintained that the Office specify where in the references that they discuss challenges relating to the methods that are claimed in the present application. Instead the references discuss problems with other methodologies that are not used in the present invention. The present invention does not have the targeting problems that are described in the cited references because ***targeting is not required*** due to the fact that macrophage cells will take up the DNA molecule. The Office has failed to provide evidence to dispute these facts.

The Clay reference discusses "Potential Use of T Cell Receptor Genes to Modify Hematopoietic Stem Cells for the Gene Therapy of Cancer." The Clay reference should not be used because it is non-analogous art. More importantly, nothing in Clay would lead one skilled in the art to conclude the claimed invention cannot be used. The experiments performed in the Clay reference were done using retroviruses (see, for example, Clay, p. 8). Clay states, "Established cell lines were transduced using retroviral supernatants." (*Id.* p. 8). The present invention uses DNA molecules, which have different properties than retroviruses, and thus will behave differently. Therefore, the Clay reference is not "acceptable evidence" to show that the methods used in the present invention are unpredictable because the methodology used and discussed in the Clay reference is dramatically different from the present invention. The Office is improperly relying upon the alleged unpredictability of one method to say that another completely unrelated method is also unpredictable. No nexus has been provided to properly apply the unpredictability of the cited references as being relevant to whether or not the enablement of the claimed invention is predictable.

The Crystal reference discusses "Transfer of Genes to Humans: Early Lessons and Obstacles to Success." The Crystal reference fails to discuss the methods in the present application. The Crystal reference focuses on "gene transfer," that requires targeting to a specific tissue. The instant claims focused on the delivery of a protein to various cells or tissues and/or modulating an individual's immune response by producing the protein from a DNA molecule. The specification discloses that macrophage cells take up DNA molecules, without the need for specific targeting means, that the protein encoded by the DNA molecule is expresses, that the macrophage migrates to the lymphnode thereby delivering the protein to the lymphnode. Therefore, the Crystal reference is not "acceptable evidence" because it fails to even discuss the techniques and concepts behind the present invention, but rather focuses on persistent gene transfer.

The Anderson reference discusses "Human Gene Therapy." As with the Clay and Crystal references, the Anderson reference fails to discuss or even mention methods related to DNA delivery methods used in the present invention. Anderson discusses the

many drawbacks of viral vectors, but fails to discuss unpredictable factors relating to non-viral vectors (*i.e.* DNA molecules and/or plasmids). Rather, Anderson supports the finding of enablement for the claimed invention stating that

> non-viral gene delivery systems will be the ***preferred*** choice in the future: safety, and ease of manufacturing. A totally synthetic gene-delivery system could be engineered to avoid the danger of producing recombinant virus or other toxic effects engendered by biologically active viral particles. Also, manufacturing a synthetic product should be less complex than using tissue culture cells as bioreactors, and QA/QC procedures should be simplified.

(Anderson, page 28, right column, emphasis added). Therefore, there is nothing in the Anderson reference that would lead one of skill in the art to question the objective truth of Applicants' specification, which includes working examples. The Anderson reference also does not rise to the level of "acceptable evidence" to show that the methods used in the present invention are unpredictable and, thus, not enabled.

In contrast to the references cited by the Office, Applicants specification has "acceptable evidence" to demonstrate that the claimed invention is enabled. Therefore, even if the cited references suggest that there are limitations to ***prior*** usages of gene delivery, which differ from the claimed invention, the instant specification provides working examples of *in vivo* delivery of a protein and/or a DNA molecule to a macrophage and/or a lymphnode according to the claimed methods.

The Office alleges that the prior art discusses only how to target a lymph node with a dye, but expressing a protein is not predictable based upon the specification. However, Applicants have demonstrated the delivery of a protein to a lymph node, to a macrophage cell, to cells of macrophage derived lineage, or to an individual (claims 1, 5, 9, 11, 25, and 29) thereby providing working examples and demonstrating that the present invention is enabled (see, for example, pages 29, 33, and 38). Applicants have provided working examples of inducing and/or modulating an immune response (claims 18 and 23) according to the methods of the present invention (see, for example, pp. 30 and 35). Therefore, one of skill in the art would follow the procedures described in Applicants' specification and at most routine experimentation to practice the claimed

invention. Without sufficient evidence to dispute the veracity of Applicants disclosure and assertions, the Office ***must*** accept Applicants' disclosure as enabling.

Accordingly, the Office's inability to provide any ***reasonable evidence*** that would cause one of skill in the art to doubt the truth of the examples in the present specification, the claimed methods are clearly enabled.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

Claims 9-17 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office alleges that claims 9-17 are indefinite because

> it is unclear as to what is meant by the term "a site on said individual's body that is proximal to said lymph node". The metes and bounds of the claimed invention are not clear because the word "proximal" is relative and an artisan would not know what is encompassed by the claimed invention.

(Office Action, page 6). Applicants respectfully disagree.

The term proximal is well defined as discussed in applicants previous response. The claimed methods can be performed by those of ordinary skill (*i.e.* trained medical professionals) who would readily know and can identify a site on an individual's body that is proximal or "nearest" to the lymph node in question as opposed to a site that is distal, or far from the lymph node in question. The location of lymph nodes are either known or are routinely determined by those of skill in the art. Persons of ordinary skill would have no difficulty in determining a site that is proximal (near) to a lymph node. A distance is not required, rather it is a general area that one of skill in the art would know that is proximal to the lymph node. It appears that the Office is rejecting the term because the term is a "relative term." However, relative terms have been found to definite by the courts. Terms, such as "about", "adjacent", and the like have all been found definite because one of skill in the art would know what is meant by the terms. The specification describes injecting proximal to a lymph node and studying the lymph

node that is "proximal to the site of injection" (Specification, page 33). Accordingly, the claims are definite within the meaning of §112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

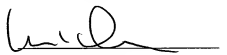
Claim 12 is allegedly indefinite because it allegedly does not further the limit the invention of claim 9. Applicants have cancelled claim 12 rendering the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Mark DeLuca
Reg. No. 33,229

DATE: February 15, 2005

COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-2000
Facsimile: (215) 701-2029